Clinical Investigations

Respiration

Respiration 2018;96:210–221
DOI: 10.1159/000488358

Received: January 25, 2018
Accepted after revision: March 11, 2018
Published online: May 16, 2018

Predictive Factors for the Long-Term Deterioration of Pulmonary Function in Interstitial Lung Disease Associated with Anti-Aminoacyl-tRNA Synthetase Antibodies

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Keywords

Antisynthetase syndrome · Interstitial lung disease · Long-term disease behavior · Middle lobe traction bronchiectasis

Abstract

Background: Little has been reported on long-term pulmonary function trends among patients with interstitial lung disease associated with anti-aminoacyl-tRNA synthetase antibodies (ARS-ILD). ***Objectives:*** To clarify the factors predictive of progression in ARS-ILD based on patients' initial clinical and radiological features. ***Methods:*** The clinical courses of 88 patients with >1 year of follow-up data on pulmonary function tests (PFTs) were retrospectively analyzed. Disease behavior was categorized into three groups: (1) improved or (2) worsened (defined as increases or decreases, respectively, of >10% in forced vital capacity and >15% in %diffusing capacity of lung carbon monoxide) or (3) stable based on PFT changes compared between 1-year results as the initial data and results at 3 years to assess the long-term course. ***Results:*** In the initial course of 75 patients with ARS-ILD who received anti-inflammatory therapy within 6 months after diagnosis, 48 patients (64.0%) improved and 6 patients (8.0%) worsened. The radiological patterns in the patients with ARS-ILD included nonspecific interstitial pneumonia (NSIP) in 46.7% and NSIP with organizing pneumonia overlap in 52.0% of the cases. One-third of the initially improved patients who worsened over the long-term course were assigned to the unstable group. By multivariate logistic analysis, middle lobe traction bronchiectasis was a significant predictive factor for the patients in the unstable

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group. ***Conclusions:*** Most patients with ARS-ILD receiving anti-inflammatory therapy had improved or remained stable in the first year. However, over the long-term course, some patients worsened despite their initial improvement. Even though the extent of the disease is limited, middle lobe traction bronchiectasis in ARS-ILD may be a useful predictor of poor long-term disease behavior.

Introduction

Anti-aminoacyl-tRNA synthetase (anti-ARS) antibodies are known to be specific to polymyositis (PM)/dermatomyositis (DM) [1–3]. Among patients with anti-ARS antibodies there is a high frequency of interstitial lung disease (ILD) (ARS-ILD) (range: 71–100%) [2]. Previous reports have indicated that the clinical characteristics are similar in PM/DM-associated ILD and in ARS-ILD without PM/DM [4, 5]. Although some patients with rapidly progressive ARS-ILD have a poor prognosis in the short run, their overall prognosis is relatively good [6, 7]. However, because of frequent recurrence and ARS-ILD refractory to therapy, some patients progress to pulmonary fibrosis over the long run despite initial improvement [8–10]. Some patients are forced to use home oxygen therapy, while a few undergo lung transplantation in clinical practice.

It is not known which subgroup of patients with ARS-ILD will suffer long-term deterioration. Therefore, this study aimed to clarify the factors predictive of long-term progression of deteriorating pulmonary function in ARS-ILD from the viewpoint of the patients' initial clinical and radiological features.

Subjects and Methods

Study Sample

Our study included 129 consecutive patients diagnosed with ARS-ILD between January 1996 and March 2017 at the Kanagawa Cardiovascular and Respiratory Center. Of those, we excluded 41 patients: 29 who were diagnosed after initiation of medication at another hospital, 11 lacking more than 1 year of follow-up data, and 1 who died within the first year. Thus, 88 patients with clinical, physiological, and radiological data collected for more than 1 year were examined.

The diagnosis of PM/DM was made by rheumatologists according to the criteria of Bohan and Peter [11]. Patients with definite, probable, or possible PM/DM were included in the study. Patients diagnosed as having interstitial pneumonia with autoimmune features (IPAF) fulfilled the criteria of the ERS/ATS task force [12]. ILD onset was classified into two types, (1) an acute/subacute form (rapidly progressive ILD showing deterioration within 3 months) and (2) a chronic form (slowly progressive presentation with gradual deterioration over a period of >3 months), according to previous reports [13, 14].

Data Collection

Baseline clinical measurements were obtained within 3 months of the initial diagnosis of ILD at our hospital. A broad panel of autoantibodies was evaluated as part of the initial workup or during the follow-up period. For ARS antibodies (anti-Jo-1, EJ, PL-7, PL-12, OJ, and KS antibodies), routine conserved serum of each patient was analyzed by RNA immunoprecipitation and protein immunoprecipitation assays at the Tokai University School of Medicine, Isehara, Japan.

Radiological Analysis

Two experienced thoracic radiologists (T. Iwasawa and S. Iso) reviewed all high-resolution computed tomography (HRCT) scans for consensus about the diagnosis of ILD in our hospital without knowledge of the patients' clinical data. The HRCT patterns were classified into nonspecific interstitial pneumonia (NSIP), organizing pneumonia (OP), usual interstitial pneumonia, and NSIP with OP overlap according to previous reports [6, 15]. NSIP with OP overlap was identified when consolidations were superimposed on a background of ground-glass opacity (GGO) with or without reticulations or traction bronchiectasis [6]. The HRCT findings were interpreted according to the recommendations of the Fleischner Society [16]. Disagreements between the two radiologists after the initial assessment were resolved by discussion.

Pulmonary Function Tests

Changes in results of pulmonary function tests (PFTs) are presented as the percentage change between the initial value and that measured at 1 year (including at 1 year ± 6 months). Patients were assigned to the "improved" or "worsened" group based on increases or decreases, respectively, of >10% in forced vital capacity (FVC) and >15% in %diffusing capacity of the lung for carbon monoxide (%DLCO) [17]. Patients who did not meet the criteria for the improved or worsened group were assigned to the "stable" group. In addition, changes in the PFT results of the patients who received anti-inflammatory therapy (i.e., corticosteroid, cyclosporine, and tacrolimus) within 6 months after ILD diagnosis were also analyzed at 3 years, and the results were compared with those at 1 year. Changes in FVC and %DLCO at 3 years (including at 3 years ± 6 months) in the patients of the improved group at 1 year were compared with the 1-year PFT results to assess long-term disease behavior. These patients were subsequently categorized into two subgroups: a "stabilization" group, which included stable patients, and an "unstable" group, which included patients who worsened after having initially shown improvement at 1 year.

Statistical Methods

Categorical baseline characteristics are summarized by frequency and percentage, and continuous characteristics are reported as the mean ± SD or median (IQR). To detect differences between groups, Fisher's exact test, one-way ANOVA, or the Mann-Whitney U test was used as appropriate. Regarding the HRCT findings, the κ value was calculated for agreement between the two thoracic radiologists for the baseline read. Next, we performed a

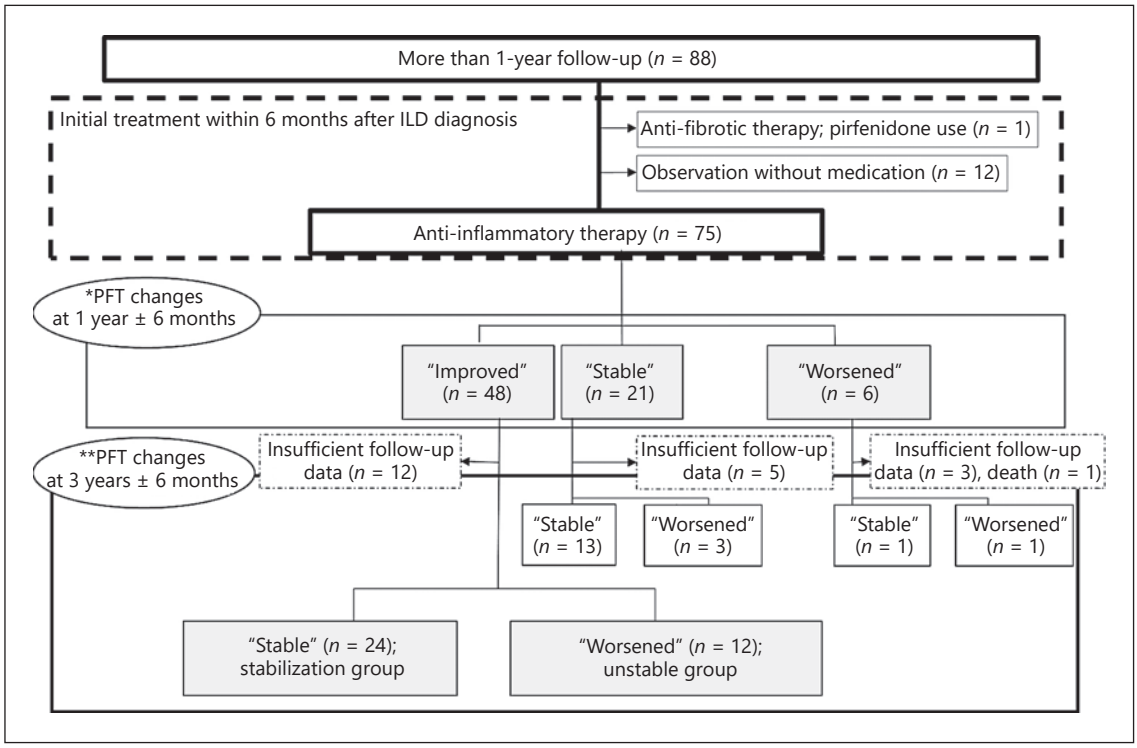


Fig. 1. Clinical courses of the patients with positive anti-aminoacyl-tRNA synthetase antibodies and ILD. ILD, interstitial lung disease; PFT, pulmonary function test.

logistic regression analysis to identify the predictive factors associated with the improved and worsened groups at 1 year, which was considered as the "initial course." Thereafter, the variables that achieved a modest level of statistical significance ($p < 0.1$ on univariate analysis) based on the forced entry method were assessed in multivariate analysis. We also performed logistic regression analysis using the same methods to identify the predictive factors associated with the unstable group at 3 years to assess long-term deterioration. We considered $p < 0.05$ to represent statistical significance in all analyses. All data were analyzed with SPSS version 22.0 (IBM Japan, Tokyo, Japan).

Results

Overall Patient Characteristics

A total of 88 patients were available after a more than 1-year follow-up period (mean follow-up period: 5.7 ± 3.8 years; 5- and 10-year overall survival using the Kaplan-Meier method was 97.0 and 83.0%, respectively). Of these, 12 patients under careful observation without medication and 1 patient who received only antifibrotic therapy (pirfenidone) were excluded (Fig. 1). The clinical characteristics of the remaining 75 patients with ARS-ILD who received anti-inflammatory therapy within 6 months after the ILD diagnosis are summarized in Table 1.

This anti-inflammatory therapy was continued during the follow-up period in all these patients. The improved group comprised 48 patients (64.0%), the stable group 21 patients (28.0%), and the worsened group 6 patients (8.0%). During the follow-up period, 40.0% of the diagnoses included connective tissue diseases (CTDs) such as PM (10.7%), DM (22.7%), primary Sjögren syndrome (5.3%), and systemic sclerosis-PM overlap (1.3%). During their follow-up period (range: 0.75–9.0 years), 11 patients developed manifestations of CTD, and these patients were also included as CTD subjects. Forty-five other patients fulfilled the criteria for IPAF, including 30 patients with positive clinical domains, i.e., distal fissuring (13 patients), distal digital tip ulceration (2 patients), inflammatory arthritis or polyarticular morning joint stiffness >60 min (7 patients), palmar telangiectasia (5 patients), Raynaud's phenomenon (5 patients), unexplained digital edema (4 patients), and unexplained fixed rash on the digital extensor surfaces (4 patients).

FVC was significantly lower in the patients in the improved group versus the other groups ($p = 0.004$), and

Table 1. Baseline characteristics at the diagnosis of anti-ARS antibody-associated ILD in patients after an initial treatment response

Characteristics	All subjects	Initial treatment response			*p* value
		improved	stable	worsened	
Patients, *n*	75	48	21	6	
Female, *n* (%)	49 (65.3)	31 (64.6)	14 (66.7)	4 (66.7)	>0.999
Age, years	60.2±10.8	61.4±9.2	57.3±12.8	60.2±15.3	0.361
Never-smokers, *n* (%)	42 (56.0)	26 (54.2)	11 (52.4)	5 (83.3)	0.440
ILD onset (acute/subacute), *n* (%)	38 (50.7)	26 (54.2)	8 (38.1)	4 (66.7)	0.354
Anti-ARS antibody (Jo-1/EJ/PL-7/PL-12/OJ/KS), *n*	19/29/10/3/2/12	12/20/7/2/2/5	5/7/3/1/0/5	2/2/0/0/0/2	0.869
Diagnosis (during follow-up period)					
(PM/DM/IPAF/others[a]), *n*	8/17/45/5	4/8/34/2	3/8/8/2	1/1/3/1	0.102
CK, IU/L	94.0 [59.0, 209.0]	77.0 [53.0, 194.0]	113.0 [82.0, 219.0]	88.0 [67.3, 264.0]	0.346
CRP, mg/dL	0.30 [0.09, 0.89]	0.40 [0.09, 1.32]	0.14 [0.06, 0.46]	0.75 [0.11, 2.19]	0.085
KL-6, U/mL	1,297.0 [903.0, 2,066.0]	1,393.5 [969.3, 2,497.0]	1,063.0 [759.0, 1,731.5]	1,471.0 [983.0, 2,227.0]	0.276
SP-D, ng/mL	192.5 [135.3, 260.7]	190.4 [131.2, 265.4]	200.2 [127.5, 270.8]	211.3 [154.5, 269.3]	0.923
Positive anti-SS-A antibody, *n* (%)	26 (34.7)	19 (39.6)	6 (28.6)	1 (16.7)	0.470
PFT results					
%FVC	73.7±16.8	69.0±16.0	82.8±13.5	78.7±21.3	**0.004***
FEV_1/FVC ratio	79.4±7.4	79.9±8.1	79.2±6.7	76.8±3.3	0.624
%DLCO	71.3±20.0	67.0±17.4	81.2±23.1	69.9±17.6	**0.028***
HRCT pattern, *n* (%)					
NSIP	35 (46.7)	19 (39.6)	13 (61.9)	3 (50.0)	
NSIP with OP overlap	39 (52.0)	28 (58.3)	8 (38.1)	3 (50.0)	0.415
OP	1 (1.3)	1 (2.1)	0 (0.0)	0 (0.0)	
Initial treatment within 6 months, *n* (%)					
Corticosteroids alone	21 (28.0)	9 (18.8)	11 (52.4)	1 (16.7)	
Corticosteroids + CyA or TAC	52 (69.3)	39 (81.3)	8 (38.1)	5 (83.3)	**0.002***
Corticosteroids + pirfenidone	2 (2.7)	0 (0.0)	2 (9.5)	0 (0.0)	
Add-on cyclophosphamide	3 (4.0)	3 (6.3)	0 (0.0)	0 (0.0)	0.649
Number of deaths (follow-up years)	10 (6.93 [1.46–12.2])	6 (11.0 [6.0–12.2])	3 (6.3 [2.9–7.0])	1 (1.46)	
Cause of death, *n*					
Respiratory failure	4	3	1	0	
Heart failure	1	1	0	0	
Malignancy	3	1	2	0	
Unknown	1	1	0	1	

Values are presented as the mean ± SD or median [IQR] unless specified otherwise. Bold type denotes significance. ILD, interstitial lung disease; ARS, aminoacyl-tRNA synthetase; PM, polymyositis; DM, dermatomyositis; IPAF, interstitial pneumonia with autoimmune features; CK, creatine kinase; CRP, C-reactive protein; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein D; PFT, pulmonary function test; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; HRCT, high-resolution computed tomography; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; CyA, cyclosporine; TAC, tacrolimus. * $p < 0.05$. [a] "Others" includes cases with primary Sjögren syndrome ($n = 4$) and systemic sclerosis-PM overlap syndrome ($n = 1$).

Table 2. Baseline characteristics at the diagnosis of anti-ARS antibody-associated ILD in the patients over the long-term course

Characteristics	All subjects	PFT changes at 3 years vs. those at 1 year		*p* value
		improved (stabilization group)	worsened (unstable group)	
Patients, *n*	36	24	12	
Female, *n* (%)	23 (63.9)	14 (58.3)	9 (75.0)	0.468
Age, years	59.7±9.2	58.9±9.6	61.4±8.4	0.442
Never-smokers, *n* (%)	18 (50.0)	9 (37.5)	9 (75.0)	0.075
ILD onset (acute/subacute), *n* (%)	20 (55.6)	12 (50.0)	8 (66.7)	0.481
Anti-ARS antibody (Jo-1/EJ/PL-7/PL-12/OJ/KS), *n*	9/14/6/2/0/5	4/11/3/1/0/5	5/3/3/1/0/0	0.142
Diagnosis (during follow-up period) (PM/DM/IPAF/others[a]), *n*	2/7/26/1	1/3/19/1	1/4/7/0	0.336
CK, IU/L	88.0 [54.8, 254.0]	78.5 [51.5, 130.3]	133.0 [62.8, 482.0]	0.261
CRP, mg/dL	0.30 [0.09, 1.21]	0.19 [0.09, 0.76]	0.48 [0.09, 1.61]	0.650
KL-6, U/mL	1,282.0 [970.5, 2,497.0]	1,414.5 [960.0, 2,765.5]	1,102.0 [971.3, 2,180.5]	0.638
SP-D, ng/mL	183.5 [128.2, 263.3]	196.7 [154.0, 386.1]	143.6 [95.7, 183.5]	**0.004***
Positive anti-SS-A antibody, *n* (%)	14 (38.9)	10 (41.7)	4 (33.3)	0.727
PFT results				
%FVC	70.0±15.8	72.3±15.6	65.4±16.0	0.221
FEV_1/FVC ratio	79.9±8.4	77.5±8.7	84.7±5.5	**0.013***
%DLCO	67.7±18.1	69.9±17.9	61.0±18.2	0.233
Initial treatment within 6 months, *n* (%)				
Corticosteroids alone	7 (19.4)	6 (25.0)	1 (8.3)	0.384
Corticosteroids + CyA or TAC	29 (80.6)	18 (75.0)	11 (91.7)	
Add-on cyclophosphamide	2 (5.6)	0 (0.0)	2 (16.7)	0.105

Values are presented as the mean ± SD or median [IQR] unless specified otherwise. Bold type denotes significance. ARS, aminoacyl-tRNA synthetase; ILD, interstitial lung disease; PM, polymyositis; DM, dermatomyositis; IPAF, interstitial pneumonia with autoimmune features; CK, creatine kinase; CRP, C-reactive protein; KL-6, Krebs von den Lungen-6; SP-D, surfactant protein D; PFT, pulmonary function test; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; CyA, cyclosporine; TAC, tacrolimus. * $p < 0.05$. [a] "Others" includes 1 case of primary Sjögren syndrome ($n = 1$).

%DLCO was significantly lower in the patients in the improved and worsened groups versus the stable group ($p = 0.028$). As initial treatment with anti-inflammatory therapy within 6 months of diagnosis, corticosteroid use alone was more highly prevalent among the patients in the stable group, whereas the use of combination therapy (corticosteroids plus cyclosporine or tacrolimus) was more highly prevalent among the patients in the improved and worsened groups ($p = 0.002$).

The HRCT pattern included NSIP with OP overlap in 52.0%, NSIP in 46.7%, and OP in 1.3% of the cases, and no patients had usual interstitial pneumonia. Interobserver agreement on the HRCT pattern was good ($\kappa = 0.886$; 95% CI: 0.762–1.000). The frequencies of the various HRCT findings are summarized in the online supplementary Table (for all online suppl. material, see www.karger.com/doi/10.1159/000488358). Most patients had findings such as GGO, reticulation, traction bronchiectasis, lower-lobe volume loss, and lower-lobe predominance.

Patient Characteristics in the Improved Group after Initial Anti-Inflammatory Therapy according to Changes in Available PFT Results over the 3-Year Follow-Up Period

Of the 48 patients in the improved group with PFT results at 1 year, 12 patients were excluded because of insufficient follow-up data, such as there being no available PFT results over the 3-year follow-up period. The remaining 36 patients were classified into two subgroups according to the PFT changes at 3 years compared to the results obtained at 1 year: a stabilization group ($n = 24$) and an unstable group ($n = 12$). As shown in Table 2, the serum surfactant protein D level was significantly lower in the unstable group ($p = 0.004$), and the FEV_1/FVC ratio was significantly lower in the stabilization group ($p = 0.013$). HRCT findings of traction bronchiectasis in the right middle lobe or lingual lobe (known as middle lobe traction bronchiectasis) were more frequent in the unstable group ($p = 0.033$) (Table 3).

Table 3. HRCT findings of anti-ARS antibody-associated interstitial lung disease in the patients over the long-term course

Characteristics	All subjects	PFT changes at 3 years vs. those at 1 year		*p* value
		improved (stabilization group)	worsened (unstable group)	
Patients, *n*	36	24	12	
HRCT pattern, *n* (%)				
NSIP	14 (38.9)	9 (37.5)	5 (41.7)	
NSIP with OP overlap	21 (58.3)	15 (62.5)	6 (50.0)	0.428
OP	1 (2.8)	0 (0.0)	1 (8.3)	
Predominant distribution (BVB/peripheral/random), *n*	34/1/1	23/1/0	11/0/1	0.562
Right upper lobe/left superior lobe, *n* (%)				
GGO	29 (80.6)	19 (79.2)	10 (83.3)	>0.999
Consolidation	3 (8.3)	2 (8.3)	1 (8.3)	>0.999
Reticulation	26 (72.2)	17 (70.8)	9 (75.0)	>0.999
Traction bronchiectasis	6 (16.7)	3 (12.5)	3 (25.0)	0.378
Right middle lobe/lingula of left lung, *n* (%)				
GGO	34 (94.4)	22 (91.7)	12 (100.0)	0.543
Consolidation	11 (30.6)	7 (29.2)	4 (33.3)	>0.999
Reticulation	32 (88.9)	20 (83.3)	12 (100.0)	0.278
Traction bronchiectasis	17 (47.2)	8 (33.3)	9 (75.0)	**0.033***
Right and left lower lobe, *n* (%)				
GGO	34 (94.4)	23 (95.8)	11 (91.7)	>0.999
Consolidation	27 (75.0)	17 (70.8)	10 (83.3)	0.685
Reticulation	36 (100.0)	24 (100.0)	12 (100.0)	–
Traction bronchiectasis	36 (100.0)	24 (100.0)	12 (100.0)	–
Honeycomb, *n* (%)	0 (0.0)	0 (0.0)	0 (0.0)	–
Lower-lobe volume loss, *n* (%)	35 (97.2)	23 (95.8)	12 (100.0)	>0.999
Lower-lobe predominance, *n* (%)	35 (97.2)	23 (95.8)	12 (100.0)	>0.999
Emphysema, *n* (%)	9 (25.0)	8 (33.3)	1 (8.3)	0.219
Cyst, *n* (%)	6 (16.7)	6 (25.0)	0 (0.0)	0.079
Enlarged mediastinal lymph node, *n* (%)	5 (13.9)	3 (12.5)	2 (16.7)	>0.999
Pleural thickening or irregularity, *n* (%)	7 (19.4)	4 (16.7)	3 (25.0)	0.664

Bold type denotes significance. ARS, aminoacyl-tRNA synthetase; PFT, pulmonary function test; HRCT, high-resolution computed tomography; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; BVB, bronchovascular bundle; GGO, ground-glass opacity. * $p < 0.05$.

Factors Predictive of Response to Initial Anti-Inflammatory Therapy according to 1-Year PFT Results

Lower FVC or %DLCO and combination therapy (corticosteroids plus cyclosporine or tacrolimus) were significant predictors of improvement over the initial course by univariate logistic analysis. However, a negative finding of lower-lobe volume loss was a significant predictor of worsening over the initial course. None of these factors remained a significant predictor in the multivariate logistic regression analysis (Table 4).

Factors Predictive of Long-Term Deterioration (Unstable Group) in the Improved Group after Initial Anti-Inflammatory Therapy

By univariate logistic analysis, a smoking habit, lower level of surfactant protein D, higher FEV_1/FVC ratio, and middle lobe traction bronchiectasis were significant predictors of unstable disease over the long-term clinical course (Table 5). Of these factors, middle lobe traction bronchiectasis was the only significant factor predictive of unstable disease by multivariate logistic analysis ($p = 0.041$). As shown in Figure 2, specific patients with ARS-ILD with middle lobe traction bronchiectasis showed improvement with initial therapy, but afterwards they deteriorated as radiologically identified fibrotic disease ex-

Table 4. Multivariate analysis of factors predictive of the initial response (improved and worsened) ($p < 0.1$ in univariate analysis)

Variable	Improved		
	Odds ratio	95% CI	*p* value
PFT results			
%FVC	0.970	0.926–1.016	0.203
%DLCO	0.995	0.955–1.037	0.825
HRCT findings			
Right upper lobe/left superior lobe			
GGO	1.990	0.532–7.439	0.307
Reticulation	1.553	0.432–5.575	0.500
Right and left lower lobe			
Consolidation	1.901	0.531–6.805	0.324
Lower-lobe volume loss	6.803	0.574–80.560	0.128
Initial treatment within 6 months			
Corticosteroids alone	1.000	reference	
Corticosteroids + CyA or TAC	2.449	0.616–9.735	0.203
Variable	Worsened		
	Odds ratio	95% CI	*p* value
HRCT findings			
Lower-lobe volume loss	0.121	0.009–1.638	0.112
Lower-lobe predominance	0.500	0.013–19.562	0.711

CI, confidence interval; PFT, pulmonary function test; FVC, forced vital capacity; DLCO, diffusing capacity of the lung for carbon monoxide; HRCT, high-resolution computed tomography; GGO, ground-glass opacity; CyA, cyclosporine; TAC, tacrolimus.

tended over the long-term course. However, some patients without middle lobe traction bronchiectasis improved and remained stable over the long-term course (Fig. 3).

Discussion

The present study revealed that two-thirds of the patients with ARS-ILD who had received anti-inflammatory therapy showed improvement in their PFT results at 1 year, but one-third of these patients had deteriorated by 3 years. In other words, even in ARS-ILD patients showing a good response to initial therapy, pulmonary function frequently deteriorated during long-term follow-up. In terms of survival, only 2 patients died within 5 years from the ARS-ILD diagnosis and the 5-year survival rate was 97.0%, which indicates relatively good survival of ARS-ILD patients, similar to that reported in previous studies [6, 7]. Importantly, some patients with ARS-ILD suffered from refractory ILD over the long run, which led to a number of adverse events such as the necessity of home oxygen therapy and side effects related to the inability to reduce the dose of corticosteroids (e.g., muscle weakness, opportunistic infection, and diabetes mellitus).

Which subgroup of ARS-ILD patients showed long-term deterioration? The radiological analysis made in our study showed that middle lobe traction bronchiectasis was a significant predictor of long-term deterioration. Typical radiological findings for ARS-ILD are GGO, reticulation, traction bronchiectasis, lower-lobe volume loss, and disease predominantly distributed in the lower lobe [9, 18]. The HRCT features were consistent with NSIP or NSIP with OP overlap in most of our subjects, though NSIP with OP overlap is not usually considered as a distinct HRCT pattern in ILD [19]. Although NSIP with OP overlap in rapidly progressive ARS-ILD may become resistant to therapy [15, 18], we could not definitively conclude this based on our relatively small cohort. Kotani et al. [20] reported that middle lobe GGO exten-

Table 5. Factors predictive of long-term deterioration (unstable group) according to logistic regression analysis

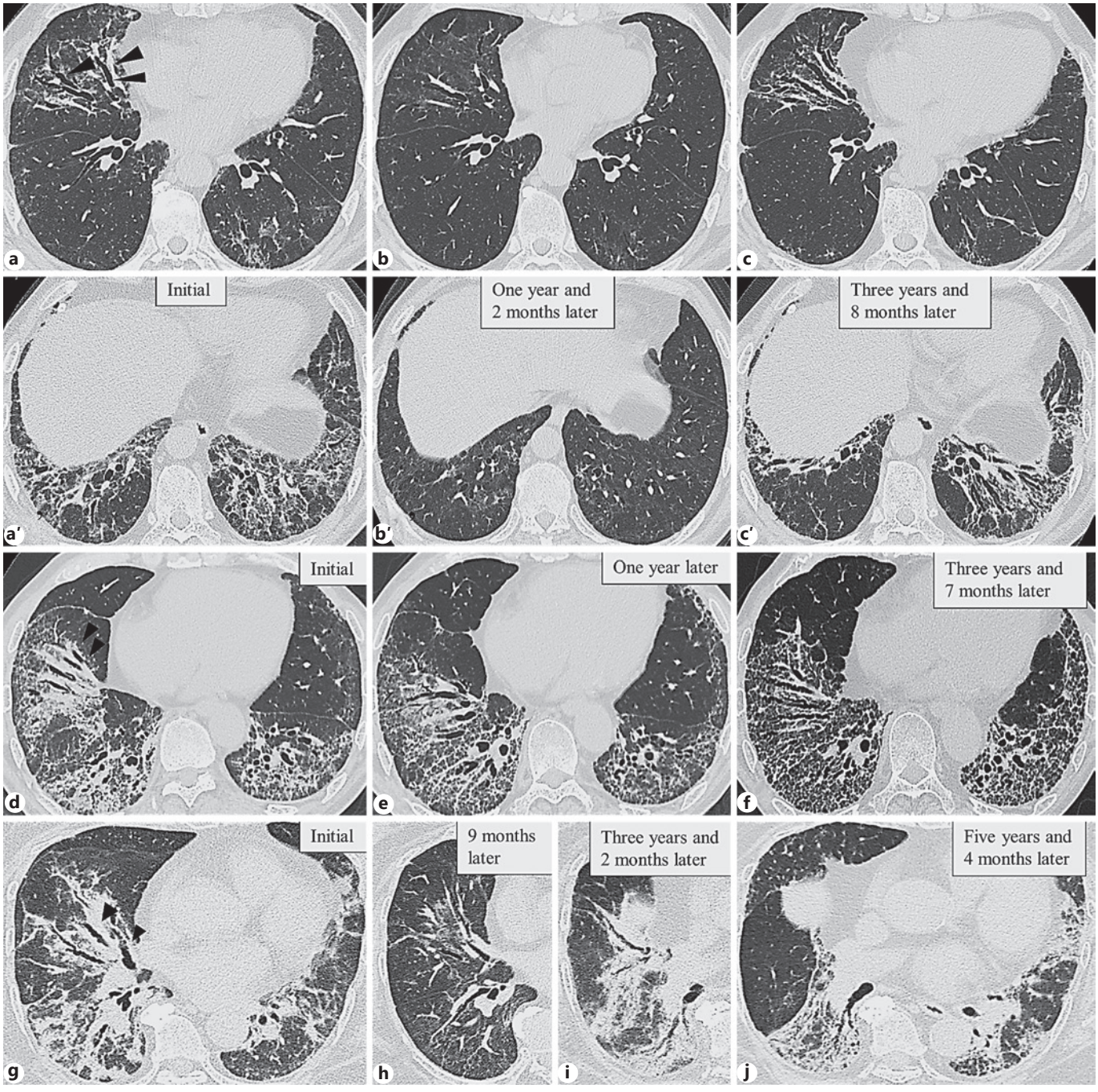
Variable	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	*p* value	Odds ratio	95% CI	*p* value
Age	1.032	0.954–1.116	0.431			
Male sex	0.467	0.100–2.173	0.331			
Current or ex-smoker	0.200	0.043–0.939	**0.041***	0.747	0.040–14.020	0.845
Chronic form (ILD onset)	0.500	0.118–2.116	0.346			
Anti-ARS antibody (reference: Jo-1)	1.000	reference				
EJ	0.218	0.035–1.364	0.103			
PL-7	0.800	0.101–6.347	0.833			
PL-12	0.800	0.037–17.196	0.887			
Diagnosis (reference: PM)	1.000	reference				
DM	1.333	0.057–31.121	0.858			
IPAF	0.368	0.020–6.723	0.500			
SP-D	0.986	0.973–0.999	**0.036***	0.982	0.953–1.011	0.211
Positive anti-SS-A antibody	0.700	0.164–2.981	0.629			
%FVC	0.970	0.925–1.018	0.218			
FEV_1/FVC ratio	1.376	1.095–1.729	**0.006***	1.351	0.984–1.854	0.063
%D_{LCO}	0.971	0.924–1.019	0.229			
Initial treatment within 6 months						
Corticosteroids alone	1.000	reference				
Corticosteroids + CyA or TAC	3.667	0.388–34.368	0.257			
HRCT pattern (reference: NSIP)	1.000	reference				
NSIP with OP overlap	0.720	0.170–3.058	0.656			
Right middle lobe/lingula of left lung						
Traction bronchiectasis	6.000	1.263–28.498	**0.024***	19.635	1.129–341.540	**0.041***
Emphysema	0.182	0.020–1.667	0.132			

Bold type denotes significance. CI, confidence interval; ILD, interstitial lung disease; ARS, aminoacyl-tRNA synthetase; PM, polymyositis; DM, dermatomyositis; IPAF, interstitial pneumonia with autoimmune features; SP-D, surfactant protein D; FVC, forced vital capacity; D_{LCO}, diffusing capacity of the lung for carbon monoxide; CyA, cyclosporine; TAC, tacrolimus; HRCT, high-resolution computed tomography; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia. * $p < 0.05$.

sion indicated a significantly poor prognosis for patients with acute or subacute ILD with DM. Following this report, because the disease distribution of ARS-ILD showed lower-lobe predominance, we hypothesized that detailed analysis not only of the lower lobe but also of the upper and middle lobes would be important. Notably, our study showed that middle lobe traction bronchiectasis was a predictor of poor long-term pulmonary function change, as shown in the examples in Figure 2. Debray et al. [9] mentioned that consolidations decrease or disappear in most cases but the disease may progress to fibrosis in more than one-third of patients. The presence of this finding with a varying extent of disease (i.e., consolidation, GGO, and reticulation) may be related to the possibility of irreversible pulmonary fibrosis. Interestingly, all 6 patients with worsened PFT results at 1 year had this finding (see the online suppl. Table). Because this finding led to a statistical error in the logistic regression analysis, it could not be determined whether this was a factor predictive of worsening over the initial course. Taken together, middle lobe traction bronchiectasis in ARS-ILD may indicate the possibility of a deterioration of pulmonary function in both the short and the long term. Conversely, even in instances of a wide extent of disease, a negative finding of middle lobe traction bronchiectasis in ARS-ILD may lead to a good response and long-term stabilization.

Our study could not discover a link between individual anti-ARS antibodies and the long-term clinical course of ILD, in contrast to previous reports on an association between worse prognosis and anti-PL-7 antibody [14, 21]. This is because the lower frequency of PM/DM and the higher frequency of IPAF in our cohort may have led to results different from those of previous studies.

Many immunosuppressive drugs have been evaluated in ARS-ILD [22–24]. Previous studies have shown that combination therapy improved the findings of PFTs and chest HRCT scans in acute or subacute progressive PM/DM-ILD [22, 25–27]. We previously reported the importance of combination therapy, which should be on the list of options to prevent relapse in anti-EJ ILD [10]. However, it is controversial whether all ARS-ILD patients need corticosteroids in addition to the other immunosuppressive drugs they are taking. In our study, this combination therapy was a significant predictor of initial improvement in the univariate analysis, but it had no influence on long-term change in pulmonary function. Although careful management is required due to the potential risk of opportunistic infection, our findings suggest that a more aggressive therapy may be required for



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ARS-ILD patients presenting with middle lobe traction bronchiectasis because of the possibility of a poor outcome of ILD over the long run.

Our study has two limitations. First, it is a single-institution, retrospective study. Second, selection bias may be present, because this study was performed in a single center specializing in respiratory disease and some of the patients were excluded from the long-term analysis because of insufficient follow-up data.

In conclusion, most patients with ARS-ILD receiving anti-inflammatory therapy improved or remained stable in the first year. However, over the long run, the course of some patients deteriorated despite showing improvement initially. Even though the extent of disease is limit-

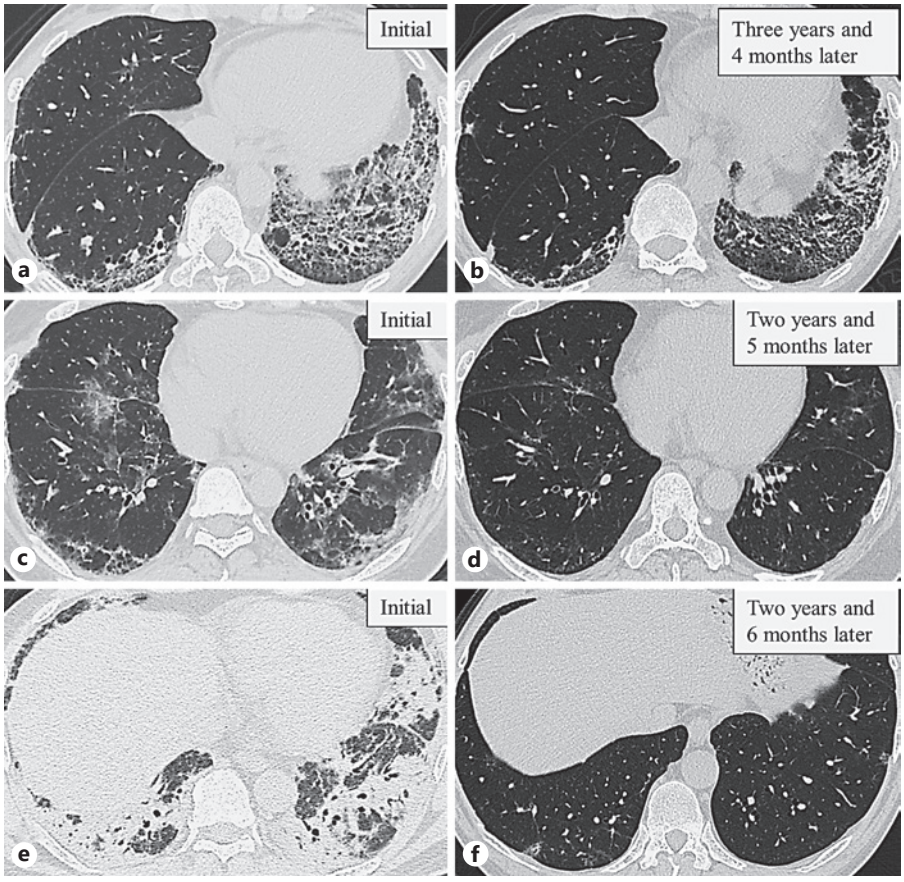

Fig. 3. Patients without traction bronchiectasis in the middle or lingual lobe. **a** High-resolution computed tomography (HRCT) scan of a 40-year-old woman positive for anti-EJ antibody showing ground-glass opacities (GGOs) with reticulation and traction bronchiectasis in the lower lobes, but these lesions were not seen in the middle lobe and lingula. **b** The same patient 3 years and 4 months later. HRCT showed improvement of the GGOs and disease extension. **c** HRCT scan of a 50-year-old woman positive for anti-PL-7 antibody showing GGOs predominantly in the lower lung. **d** The same patient 2 years and 5 months later. HRCT showed marked improvement of the abnormal shadows. **e** HRCT scan of a 56-year-old man positive for anti-Jo-1 antibody showing consolidation along with bronchovascular bundle and lower-lobe volume loss, findings compatible with nonspecific interstitial pneumonia with an organizing pneumonia overlap pattern. **f** The same patient 2 years and 6 months later. HRCT showed dramatic improvement of the abnormal findings.

Fig. 2. Middle lobe traction bronchiectasis. **a–c** Radiological time-dependent changes in a 58-year-old man with anti-Jo-1 antibody and a nonspecific interstitial pneumonia (NSIP) pattern. **a**, **a′** At the initial diagnosis, high-resolution computed tomography (HRCT) showed ground-glass opacities (GGOs) with subpleural sparing predominantly in the lower lung, and traction bronchiectasis in the middle lobe (arrowheads) and lower lobe. This traction bronchiectasis represents irregular bronchial dilatation caused by surrounding pulmonary fibrotic change. **b**, **b′** One year and 2 months later, HRCT showed a marked improvement of the traction bronchiectasis and GGOs. **c**, **c′** Three years and 8 months after the initial diagnosis, HRCT showed exacerbation mainly with reticulation, GGOs, and traction bronchiectasis, which suggested fibrotic changes. **d–f** Radiological time-dependent changes in a 72-year-old man with anti-EJ antibody and NSIP with an organizing pneumonia (OP) overlap pattern. **d** At the initial diagnosis, HRCT showed consolidations superimposed on GGOs with traction bronchiectasis (arrowheads: middle lobe traction bronchiectasis). **e** One year later, the consolidations had resolved, but GGOs with reticulation remained. **f** Three years and 7 months later, HRCT showed a moderate increase in disease extent of the reticulation and traction bronchiectasis. **g–j** Radiological time-dependent changes in a 63-year-old woman with anti-PL-7 antibody and NSIP with an OP overlap pattern. **g** At the initial diagnosis, HRCT showed mainly consolidation with GGOs with traction bronchiectasis (arrowheads). **h** Nine months later, the consolidations had disappeared. **i** Three years and 2 months later, the consolidations had relapsed. **j** Five years and 4 months later, HRCT showed regions of consolidation with lower-lobe volume loss.

ed, a positive radiological finding of middle lobe traction bronchiectasis in ARS-ILD could be a useful predictor of poor long-term disease behavior. This radiological finding may also be helpful in assessing appropriate strategies to treat ARS-ILD.

Acknowledgments

We sincerely thank Ms. Etsuko Iwata and Ms. Miyako Nakagawa of the Tokai University School of Medicine for their contribution to detecting the anti-ARS antibodies and Yosuke Sasaki of Satista Co., Ltd., for his advice on statistical analysis. The authors would like to thank Rise Japan LLC for the professional English language review.

Statement of Ethics

This retrospective cohort study was approved by the institutional review board of the Kanagawa Cardiovascular and Respiratory Center (KCRC-17-0014). Because of the retrospective nature of the study, the review board waived the need for written informed consent from the patients.

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